



Effect of *Tribulus terrestris* L. on sperm parameters in men with idiopathic infertility: A systematic review

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ABSTRACT

Background and objective(S): *Tribulus terrestris* L. is an herbal plant that has long been used as sex stimulant and to treat male infertility. This systematic review collected the clinical trials and/or quasi-experimental studies on the effect of *T. terrestris* on sperm parameters in idiopathic male infertility.

Materials and methods: To search the related articles, Cochrane Library, EMBASE, ProQuest, Clinicaltrials.gov, WHO, Google Scholar, MEDLINE via Pubmed, Web of Science, SID, Magiran, Irandoc, and Iranmedex databases were used without any time limitation. Words used to search were *T. terrestris* L., Tribestan, male infertility and sperm parameters based on the MeSH glossary. To assess the eligibility of the articles, the views of the two authors and in cases where there was no agreement, the third person was used.

Results: Through searching of the databases, 5775 articles were identified, of which 3509 were entered after removing the duplicates. Afterward, 102 articles were screened for inclusion. Finally, 7 articles were included in this systematic review. Only one quasi-experimental without control arm article reported that the use of *T. terrestris* L. in the treatment of idiopathic male infertility was not effective. In the others, *T. terrestris* L. was reported to be effective in improving some or all parameters of the sperm, namely number, motility and morphology.

Conclusion: The results of the present systematic review showed that the consumption of *T. terrestris* L., in general, resulted in the improvement of sperm parameters. This result was obtained from 6 out of the 7 articles.

1. Introduction

Infertility is defined as the disability to conceive after one year of unprotected sexual practice.¹ According to world health organization, one out of four couples is suffering from infertility.² Infertility is a medical problem and a social crisis that can cause devastating effects on social life, interpersonal communication and marital relationship.^{3–5}

Male factor has been observed in about 50% of infertility cases.⁶ Evidence has shown that the important factor in 30–80% of men's infertility is the destructive effects of active oxygen species.⁷ These components can damage sperm in either of two ways: damage the sperm membrane which could decrease the mobility and possibility of connecting to the oocyte or can damage the genetic material of the sperm.^{8–10}

At present, chemical and laboratory treatments are available for idiopathic male infertility.^{11,12}

Chemical drugs do not have significant effect on the treatment of male infertility.^{13,14} Laboratory methods are expensive and have many complications and stress.

A number of herbs have shown positive effects on the improvement of semen parameters.¹¹ These beneficial effects can be attributed to their antioxidant effects.¹⁵ Herbal medicine today in Europe, the United states,¹⁶ and especially in developing countries, has been widely used due to cultural acceptability and better fit with the body, less side effects and being non-invasive, less financial and emotional burden, more access and easy to provide.^{15,17,18}

T. terrestris L., which belong to the family of Zygophyllaceae, is a famous herb in traditional medicine in many countries.¹⁹ It is used to

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treat a number of diseases and has a long history of use in traditional Chinese medicine and Indian ayurvedic practice. *T. terrestris* L. is also known as Gokshura, Puncture Vine, Caltrop, Yellow Vine, and Goat-head. This plant is native to the Southern Europe, Southern Asia, Africa, and Northern Australia.²⁰ It has high levels of steroidal saponins and as such, a source for some drugs combinations. Currently, food supplements from this plant are sold in the United States, Europe and also in Iran.¹⁹

So far, numerous animal and human studies have been conducted on the effect of *T. terrestris* L. on male infertility, sperm motility,^{21,22} and sexual dysfunction of men^{23,24} and women.^{25,26} The product obtained from this plant known as Tribestan, is also available in global market.²⁷ The company "Sopharma" produces this drug in the tablets form of 250 mg. The recommended dosage and treatment period for men is 1–2 tablets three times a day for 90 days. The side effects of this medication include allergic reactions or gastric mucosal effects. This product contains *T. terrestris*, Microcell, Cabosil, Polyplasdone XL, Polyvinylpyrrolidone, Talc, Film coating, and Magnesium stearate.²⁸ Other products of this plant are Libilov and Androsten. The active ingredients found in Libilov are *T. terrestris*, Ginkgo Biloba and L-Arginine. The recommended dose is one to three capsules per day.²⁹

In addition to the use of this plant to treat impotence and sexual dysfunction, it can be recommended for the treatment of heart disease.³⁰ It has antimicrobial^{31,32} and anti-cancer effects^{19,33} and also protective effect in diabetes.³⁴ The pharmaceutical uses of this plant include treatment of cough, headache and mastitis. The uses of this plant, as described in traditional medicine, include treatment of abdominal distension, kidney stones, diarrhea, epistaxis and vitelligo.³⁵ The main chemical components of this plant are flavonoids, alkaloids, saponins, lignin, amides and glycosides.³⁶ Oral daily dosage is 3–6 g of the powdered crude drug as a decoction or 6–9 g in divided daily doses as a decoction. The side effects include diarrhea, chronic headaches, anxiety and acne. The contraindications to the use of this herb are allergy or hypersensitivity to this plant due to *fructus tribuli*. The use of this plant can be of crude or extract form. The preparation of aqueous extract of this plant is carried out with a sample of dried fruit from the plant using chloroform, ethyl acetate, ethanol and water at room temperature. To prepare the ethanolic extract of *T. terrestris*, the fruit is scratched and extracted using a soxhlet extraction equipment.³⁵

According to the authors search, a review study on the effect of *T. terrestris* L. on sperm parameters is yet to be conducted. Therefore, this systematic review was conducted to determine the effect of *Tribulus terrestris* L. on sperm parameters in men with idiopathic infertility.

2. Material and methods

A systematic review study was designed based on the defined guidelines (Cochrane collaboration, 2008).

2.1. Types of studies

In this systematic review, randomized clinical trials, quasi experimental or semi experimental studies were conducted in which the effects of *T. terrestris* L. on semen parameters were investigated in men with idiopathic infertility.

Types of participants and interventions:

2.2. Inclusion criteria

In the present study, all the articles including the randomized controlled trials, quasi or semi experimental studies which investigated the effect of *T. terrestris* L. on seminal parameters in idiopathic infertile men with abnormal spermograms were studied. In this survey, the PICO criterion was used that included participants, intervention, control group and the outcome. The participants included idiopathic infertile men with abnormal spermogram. The intervention included the use of

the studied plant in the forms of granules and extracts with different doses. The control group included placebo, any other known drug or without intervention.

2.3. Exclusion criteria

Men suffer infertility due to aspermia, azoospermia, genetic problems, varicocele and sexually transmitted infections.

In several articles, a combination of *T. terrestris* L. was used beside other medicinal herbs, due to the impossibility of determining the net effect of this plant.

2.4. Types of outcomes

The primary outcome was sperm parameters (number, motility, morphology) and the secondary outcome was *T. terrestris* L. side effects.

2.5. The strategy of articles search

The search for review ahead of print or published articles was done regardless of language or time limitation. References available in review articles were investigated as additional resources. Review of Persian thesis was done by searching the websites of universities in Iran. It was also attempted to search for articles published at conferences. But there was no full access to the gray literature. The search was conducted by two of the authors through:

- 1 monthly searches in the database Cochrane and Cochrane center of clinical trials (central)
- 2 weekly search in Medline
- 3 weekly search in EMBASE
- 4 weekly search in Scopus, Google Scholar, ProQuest, Science Direct
- 5 weekly search in databases such asSID, IranMedex, and Magiran.

To search for articles, the keywords used were in accordance with the MeSH glossary. The keywords that were used alone or in combination to search for articles included sperm parameters, male infertility, *T. terrestris* L. and Tribestan. In the first phase, a total of 5775 articles were collected from databases. Three thousand five hundred and nine (3509) articles remained after removing the duplicated items. Afterward, 3401 articles were screened for inclusion. Then, 3389 were excluded by title and abstract based on not being relevant to this review. Finally, out of 12 articles, 7 were reviewed (Fig. 1).

2.6. Evaluation of articles quality

The quality and acceptability of articles were evaluated by two authors (SS-NGA).

In cases where there was no agreement, the opinion of the third person (AFKH) was used and agreed upon.

2.6.1. Data extraction

A form was designed to extract data. Information related to the study were collected which included time, place, author, manner of consumption, details of comparisons between treatment regimens, duration of treatment, duration of follow up, characteristics of participants, number of participants randomized, and number of participants dropped.

2.7. Assessment of risk of bias

To review the articles in terms of selection bias, performance bias, detection bias, attrition bias and reporting bias, two authors separately performed an assessment based on Cochrane handbook.³⁷

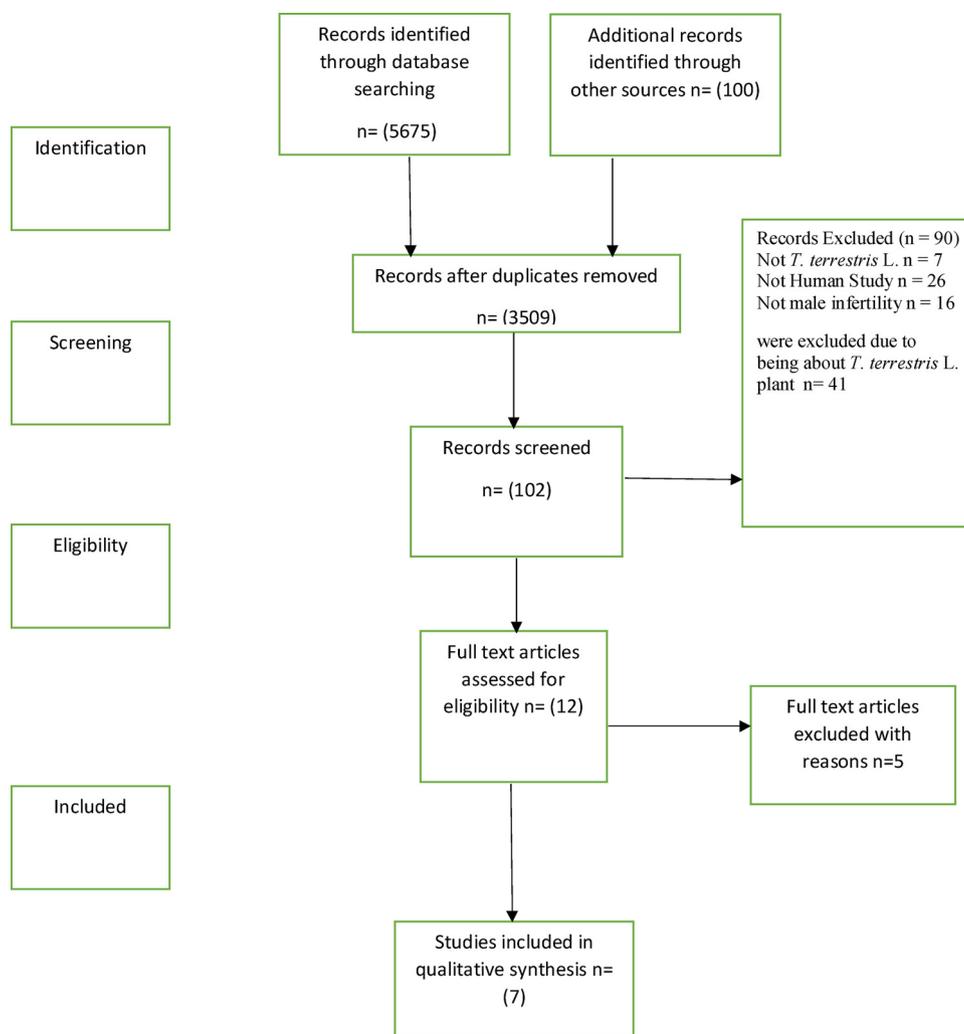


Fig. 1. Study flow diagram.

2.7.1. Random sequence generation (checking for possible selection bias)

Based on the randomization method in the articles, the three words, high risk, low risk and unknown risk, were used to determine the risk of bias in the selected articles. For example, if a computerized random numbers generation, table of random numbers for randomization, coin drop or dice throws was used, it was reported to have low risk of selection bias. But if non-random methods, such as birth date, the date of the patients admission, patient case code, doctor's or self-patient opinion or based on laboratory results, were used, they were reported to have high risk of selection bias. In cases where an explanation has not been used in relation to the method, the term unknown risk was used.

2.7.2. Allocation concealment (checking for possible selection bias)

To check the risk of allocation concealment bias, the three terms, high risk, low risk and unknown risk, were used. If a central randomization method, sequentially numbered opaque sealed envelopes, or phone assignment was used, it was reported to have low risk of selection bias, and if these methods were not used, the risk of selection bias was reported to be high. There was an unknown risk of bias in the case where information was not available.

2.7.3. Blinding of participants and personnel (checking for possible performance bias)

To check the risk of performance bias, three terms, low risk, high risk and unknown risk, were used. For articles in which both the researcher and participants were blinded, the term low risk was used,

while for the articles in which blinding was not performed, the term high risk was not used. For articles with insufficient information, the term unknown risk was used.

2.7.4. Blinding of outcome assessment (checking for possible detection bias)

To check the risk of bias of outcome assessment, the terms high risk, low risk and unknown risk were used. In cases of outcome evaluator blindness, the risk of bias was low and if not blind, the risk was reported to be high. In cases where the explanation was insufficient, an uncertain risk was reported.

2.7.5. Incomplete outcome data (checking for possible attrition bias)

The words high risk, low risk, and unclear risk were used to check the attrition bias. In cases where there was no attrition data, or there was balance between groups, the risk of bias was reported as low. If the drop was high or there was no balance between groups, the risk was reported as high. In cases where there was insufficient explanation for the bias, an unknown risk was reported.

2.7.6. Selective reporting (checking for reporting bias)

To check the reporting bias of the outcomes, three terms, high risk, low risk and unknown risk, were used. In cases where all of the already specified outcomes have been reported, the risk of bias was reported as low, and if all outcomes were not reported, or an outcome had not been specified, the risk was reported as high. In cases where the explanation was not specific enough, the risk was reported as unknown.

2.8. Data analysis

In this study, after reviewing the databases, 7 articles were finally included. But due to some reasons, such as failure to fully report data or quasi-experimental articles, no meta-analysis was possible. Studies by Roaih et al.³⁸, Salgado et al.³⁹ and Arsyad⁴⁰ could not enter the meta-analysis since they were semi-experimental. Also, a study by Ismail et al.²⁷ did not enter, because in this study, the intervention group was honey and the control group was *T. terrestris* L. Further, a study by Adimoelja et al.⁴¹ did not enter the meta-analysis due to lack of data related to the study results. While those of Sellandi et al.²¹ and Setiawan et al.⁴² were could not enter due to the percentage of relief report of the data.

As regards studies on the side effects of *T. terrestris* L., only Setiawan et al.⁴² reported no side effect.

3. Results

Clinical trials that have investigated the effect of *T. terrestris* L. on sperm parameters in idiopathic infertile men are as follows:

Sellandi et al.²¹ conducted a study to determine the effect of *Tribulus terrestris* L. fruit on oligospermia. At first, 72 eligible infertile men with oligospermia were enrolled in the study, out of which 9 were excluded from the study for unknown reasons. Eventually, the outcome was examined in 63 of them. Thirty-two patients in the intervention group received two capsules containing 6 g of *T. terrestris* L. daily for 60 days. While 31 patients in the control group received placebo capsules. All participants were aged 21–50 years and had oligospermia. None of them had aspermia, azoospermia or genetic problems such as the klinefelter, and items like genital infection, varicoceles, STDs and chronic diseases such as diabetes. Patients were followed up every two weeks during the treatment period and one month after the completion of the treatment. The results of the study showed the improvement of the semen parameters in terms of total number of sperms, morphology ($P \leq 0.001$) and RLP mobility of sperms (rapid linear progressive mobility) ($P < 0.05$) in the group that received granules of *T. terrestris* L. In the group that received *T. terrestris* L., the percentage of relief of the total number of sperm was 86.31%, sperm morphology 7.89%, sperm motility 20.1%, RLP 3.33%, SLP (slow linear progressive mobility) 7.53% and NP (with no mobility) 12.25%. In the comparison between groups, the total sperm count was found to increase in both groups and there was no significant difference between them ($P > 0.05$).

A double-blind placebo-controlled trial was conducted by Setiawan et al.⁴² with the aim of determining the effect of *T. terrestris* L. on the morphology and acrosome reaction of sperm and compare the result with the control group. Thirty men having primary and secondary infertility with oligoasthenoteratospermia (28 men with primary infertility and 2 with secondary infertility) were enrolled into the study. 15 patients in the intervention group received 500 mg of *T. terrestris* L. extract tablets three times a day for 60 days. Also, 15 participants in the control group received placebo pill (containing sugar). The volume of fluid, sperm concentration, morphology, acrosome reaction, and other parameters were evaluated before and after treatment. There was a significant increase in sperm mobility in the treated group as compared with the control group (1.666 ± 12.344 versus -9.000 ± 10.889 , $p < 0.05$). Also, the ratio of sperm with normal acrosome reactions in the treated group was increased as compared with the control group (6.633 ± 6.282 versus -0.333 ± 3.406 , $p < 0.05$). Further, the ratio of immotile sperm in the treated group was significantly lower than the control group (10.333 ± 16.198 versus 12.666 ± 21.865 , $p < 0.05$). However, in terms of volume of fluid (ml) (0.373 ± 1.102 in the treatment group versus 0.240 ± 0.783 in the control group), sperm concentration (-1.104 ± 8.157 in treated group versus -0.346 ± 7.183 in the control group), morphology (2.866 ± 5.222 in treated group versus 2.533 ± 6.058 in the control group and the percentage of sperms with fast and linear motility (1.666 ± 5.563 in

treated group versus 1.000 ± 5.732 in the control group), slow and non-linear (1.666 ± 12.344 versus -9.000 ± 10.889 of the control group), stationary motility (6.000 ± 11.052 versus -4.666 ± 20.482) and no movement (-10.333 ± 16.198 versus 12.666 ± 21.865) were not significantly different ($p > 0.05$). Side effects were not observed. In general, *T. terrestris* L. with a dose of 500 mg three times a day for 60 days showed a significant role in restoring some sperm functions, especially motility and acrosome reaction in men with oligoasthenoteratospermia.

Furthermore, a study was conducted by Ismail et al.²⁷ with the aim of determining the effectiveness of Tualang honey on sperm parameters, erectile function, hormones and immunity in comparison with the *T. terrestris* L. as the control group. As a result, 68 married, literate males within the age range of 20–55 years, with a sperm count of 5–10 million per milliliter were investigated. Thirty-four participants in intervention group received 20 g of Tualang honey daily 30 min before breakfast for 12 weeks. The other 34 patients in *T. terrestris* L. group received 250 mg of Tribestan daily for 12 weeks after a meal. The results of the study showed that there was no significant difference in the number ($P = 0.281$), motility ($P = 0.670$) and sperm morphology ($P = 0.517$) between Tualang honey group and Tribestan after intervention. The results of intra group analysis in the group that received Tribestan showed a significant difference in term of number ($P < 0.007$) and sperm morphology ($P = 0.009$) before and after intervention. There was a significant difference in Tualang honey recipient group in terms of number ($P < 0.001$), motility ($P = 0.015$) and sperm morphology ($P = 0.008$) before and after treatment.

In a double blind study by Adimoelja et al.⁴¹ in which the primary outcome of the study was not explicitly mentioned, a total of 45 married infertile men with oligoasthenoteratospermia were entered into the study, of which 36 men in the intervention group received daily 500 mg tablets of *T. terrestris* L. extract known as Libilov, for three months. While the 9 other men also received placebo (sugar pills) in the control group. The criteria for entering the study and the data related to the results were not mentioned. The results showed that there were significant increases in sperm count before and after intervention in both groups. But there was no significant difference between the groups (P value was not reported). However, improvement in sperm motility between the two groups was not observed (P value was not reported). There was an improvement in sperm morphology in the intervention group, justifying the successful pregnancies in this group. Between-group comparison was not performed. It seems that *T. terrestris* L. led to the improvement of sperm morphology and acrosome reaction and as a result, increased fertility. There was improvement in sperm morphology in the treated group (" $p > 0.05$ ").

An uncontrolled study was conducted by Roaiah et al.³⁸ with the aim of determining the effect of *T. terrestris* L. on semen parameters and serum testosterone in men with idiopathic infertility. As a result, 30 men with idiopathic infertility were included in the study and they received three tablets of 250 mg *T. terrestris* L. extract daily for three months. The age of all patients with idiopathic infertility ranged from 30 to 50 years. The results of the study showed that there was no significant difference in semen parameters [(quantity; before: 14.900 ± 23.987 , after: 17.600 ± 21.683 , $p = 0.839$), (motility; b: 20.000 ± 11.396 , a: 27.500 ± 12.525 , $p = 0.091$), and (morphology; b: 40 ± 13.352 , a: 37.500 ± 10.296 , $P = 0.290$), (PR = progressive motility; b: 5.000 ± 5.241 , a: 10.000 ± 7.512 , $P = 0.072$), (NP = non progressive; b: 15.000 ± 10.90 , a: 15.500 ± 7.512 , $P = 0.290$)], free testosterone ($P = 0.075$), total testosterone level and LH before and after treatment. It was shown that *T. terrestris* L. was not effective in the treatment of idiopathic male infertility.

A study was conducted by Salgado et al.³⁹ to determine the effect of *T. terrestris* L. on the quality of semen and biological parameters. As a result, 65 men with abnormal sperm were included in the study. All men aged 15–50 years were without hormonal malformations and

chronic diseases. Patients consumed 250 mg capsules of *Tribulus terrestris* L. extract, called Androsten, daily for 15 weeks. The results showed that after the end of the intervention period, there was a significant increase in number (before: 3.33 ± 4.22 , after: 6.40 ± 10.36 , $P = 0.007$) and motility (b: 34.85 ± 27.36 , a: 54.43 ± 38.62 , $P < 0.001$). However, the sperm morphology did not change (b: 1.50 ± 1.29 , a: 1.43 ± 1.09 , $P = 0.863$), and the Dihydrotestosterone levels (b: 469.49 ± 319.26 , a: 596.82 ± 283 , $P < 0.023$) showed a significant difference.

Furthermore, Arsyad et al.⁴⁰ conducted a study to determine the effect of the dose and the duration of the specific treatment effect of *T. terrestris* L. on the quality and quantity of sperm, as well as its effect on sexual desire, erection, ejaculation and orgasm. As a result, 15 patients within the age range of 25–40 years and with moderate idiopathic oligospermia were enrolled in the study. Participants took two Libilov three times a day. But this study did not mention the dosage of medications. In addition, the control group and the characteristics of the number of subjects, the type of the study and the nature of placebo drug were unknown. The results of the study showed an increase in the number (before: 9.89 ± 3.58 , after: 15.73 ± 3.41 , $P < 0.05$), motility (b: 24.33 ± 7.03 , a: 36.00 ± 6.32 , $P < 0.05$) and the morphology (b: 35.93 ± 4.03 , a: 43.87 ± 4.12 , $P < 0.05$) of the sperms (Table 1).

3.1. Risk of bias in articles

3.1.1. Random sequence generation (checking for possible selection bias)

In studies by Sellandi et al.²¹ and Ismail et al.²⁷ the risk of selection bias was reported as low, while in studies by Setiawan et al.,⁴² Arsyad et al.⁴⁰ and Adimoelja et al.,⁴¹ the risk of selection bias was unknown. Conversely, Salgado et al.³⁹ and Roaiah et al.³⁸ reported that this risk was high.

3.1.2. Allocation concealment (checking for possible selection bias)

From the view of allocation concealment, Sellandi et al.²¹ and Ismail et al.²⁷ reported low risk, while Setiawan et al.,⁴² Arsyad et al.⁴⁰ and Adimoelja et al.⁴¹ reported unknown risk. In studies by Salgado et al.³⁹

and also Roaiah et al.,³⁸ risk was reported as high.

3.1.3. Blinding of participants and personnel (checking for possible performance bias)

As regards the risk of performance bias, it was reported to be low by Sellandi et al.²¹, while by Setiawan et al.,⁴² it was reported to be unknown. However, in several studies by Salgado et al.,³⁹ Roaiah et al.,³⁸ Ismail et al.,²⁷ Arsyad et al.,⁴⁰ and Adimoelja et al.,⁴¹ this risk was reported to be high.

3.1.4. Blinding of outcome assessment (checking for possible detection bias)

The risk of detection bias was reported to be low by Sellandi et al.²¹, while this risk was reported to be unknown in studies by Setiawan et al.,⁴² and Adimoelja et al.⁴¹ However, in several studies by Salgado et al.³⁹ Roaiah et al.³⁸ Ismail et al.²⁷ and Arsyad et al.,⁴⁰ this risk was reported to be high.

3.1.5. Incomplete outcome data (checking for possible attrition bias)

Exposure to high risk of attrition bias was reported by Sellandi et al.²¹, Salgado et al.³⁹ and Ismail et al.²⁷ However, in studies by Setiawan et al.,⁴² Roaiah et al.³⁸ and Arsyad et al.,⁴⁰ the risk of this bias was low. While Adimoelja et al.⁴¹ reported this risk of bias to be unknown.

3.1.6. Selective reporting (checking for reporting bias)

In several studies by Sellandi et al.²¹, Setiawan et al.,⁴² Salgado et al.,³⁹ Roaiah et al.,³⁸ Ismail et al.²⁷ and Arsyad et al.,⁴⁰ risk of reporting bias was reported as low. While Adimoelja et al.⁴¹ reported this risk of bias as high. (Table 2, Figs. 2 and 3).

4. Discussion

The aim of the present review was to review the existing studies on the effect of *T. terrestris* L. on semen parameters in males with idiopathic infertility. The results of this study showed that consumption of this plant generally improved sperm parameters. Of the 7 articles, only one quasi-experimental study³⁸ without control arm reported that *T. terrestris* L. consumption was not effective in the treatment of idiopathic

Table 1

Characteristics of the studies included in systematic review with spermogram parameters.

ID	Study	Year	Country	Pts number	intervention	Control	sperm count	Morphology Mean \pm SD	Motility Mean \pm SD	adverse events
1	Adimoelja et al [41]	1995	It was not mentioned	45	500 mg Libilov tablets TDS	placebo	Not reported	Not reported	Not reported	It was not reported
2	Arsyad et al [20]	1996	Indonesia	15	2 Libilov tablets TDS	There was no control group	b: 9.89 ± 3.58 a: $15.73 \pm 3.41 \times 10^6/ml$	b: 35.93 ± 4.03 a: $43.87 \pm 4.12\%$	b: 24.33 ± 7.03 a: $36.00 \pm 6.32\%$	It was not reported
3	Ismail et al [27]	2014	Malaysia	68	250 mg Tribestan tablets TDS (This was control group in this study)	Tribulus terrestris L.	b: $12.9 \pm 4.99 \times 10^6/ml$ a: $25.3 \pm 25.14 \times 10^6/ml$	b: $40.4 \pm 3.69\%$ a: $77.3 \pm 10.86 \%$	b: $63.0 \pm 28.30\%$ a: $49.8 \pm 16.62 \%$	It was not reported
4	Roaiah et al [38]	2016	Cairo	30	250 mg Tribulus terrestris L. extract TDS	There was no control group	b: $14.900 \pm 23.987 \times 10^6/ml$ a: $17.600 \pm 21.683 \times 10^6/ml$	b: $40 \pm 13.352 \%$ a: $37.500 \pm 10.296\%$	b: $20,000 \pm 11.396 \%$ a: $27.500 \pm 12.525\%$	It was not reported
5	Salgado et al [39]	2016	Brazil	65	250 mg Tribulus terrestris L. extract capsules per day	There was no control group	b: $3.33 \pm 4.22 \times 10^6/ml$ a: $6.40 \pm 10.36\%$	b: $1.50 \pm 1.29 \%$ a: $1.43 \pm 1.09\%$	b: $34.85 \pm 27.36 \%$ a: $54.43 \pm 38.62\%$	It was not reported
6	Setiawan et al [42]	1996	Indonesia	30	500 mg Tribulus terrestris L. extract tablets TDs	Placebo	b:† a:† $-1.104 \uparrow 8.157 \times 10^6/ml$	b:† a:† $2.866 \pm 5.563\%$	b:† a:† $1.666 \pm 12.344\%$	No adverse event
7	Sellandi et al [42]	2012	Jamnagar	72	6 g Tribulus terrestris L. capsules BID	Placebo	† 86.31%	† 7.89%	† 20.1%	It was not reported

Primary Outcomes consisted of sperm count, Morphology and Motility were reported for Tribulus terrestris L. group.

^b :Baseline value a: after intervention value.

* percentage of relief in the study of Sellandi et al.

† Differences were reported in the study of Setiawan.

‡ Abnormal forms was reported in the study of Roaiah et al.

Table 2
Characteristics of included studies and their risk of bias.

		Sellandi et al (2012)
RCT		Methods
Seventy two infertile men between 21–50 years with oligospermia were divided in two groups including <i>Tribulus terrestris</i> L. group (n = 36), Placebo group (n = 36)		Participants
Intervention group: 36 participants received two granules containing 6 g of <i>Tribulus terrestris</i> L. twice a day		Interventions
Control group: 36 participants received Placebo granules similar to <i>Tribulus terrestris</i> L.		Outcomes
The percentage changes in cardinal symptoms and quality of Sexual Health questionnaire and management of oligospermia. (The management of oligospermia in this study is secondary outcome).		Results
In comparison between groups, both groups increased the total sperm count and there was no significant difference between the two groups (P > 0.05).		Risk of bias
Support for judgment	Authors' judgment	Bias
They used computer-generated randomization plan	Low risk	Random sequence generation (selection Bias).
They used the labeled drugs prepared by a department	Low risk	Allocation concealment (selection bias).
This study was a double blinded controlled trial	Low risk	Blinding of participants and personnel (performance bias).
This study was a double blinded controlled trial	Low risk	Blinding of outcome assessment (detection Bias).
There were a total of 9 excluded men due to unclear reasons	High risk	Incomplete outcome data (attrition bias).
All outcomes were reported	Low risk	Selective reporting (reporting bias).
		Setiawan (1996)
RCT		Methods
Forty infertile men between 25–40 years with oligasthenoteratospermia were divided in two groups including <i>Tribulus terrestris</i> L. group (n = 15), Placebo group (n = 15)		Participants
Intervention group: 15 participants received two tablets containing 250 mg of <i>Tribulus terrestris</i> L. three times a day		Interventions
Control group: 15 participants received Placebo tablets similar to <i>Tribulus terrestris</i> L.		Outcomes
Effect of <i>Tribulus terrestris</i> L. treatment on sperm morphology and acrosome reactions. Evaluation of ejaculate volume, sperm concentration (The management of oligospermia in this study is secondary outcome).		Results
There was a significant difference between the control and intervention groups in terms of the sperm motility (p < 0.05) but not in sperm count and morphology (p > 0.05).		Risk of bias
Support for judgment	Authors' judgment	Bias
The randomization method was not described.	unclear risk	Random sequence generation (selection Bias).
No specific information regarding allocation concealment has been given	unclear risk	Allocation concealment (selection bias).
No specific information regarding participants and personnel blinding has been given	unclear risk	Blinding of participants and personnel (performance bias).
No specific information regarding outcome assessor blinding has been given	unclear risk	Blinding of outcome assessment (detection Bias).
Minimal loss	Low risk	Incomplete outcome data (attrition bias).
All outcomes were reported	Low risk	Selective reporting (reporting bias).
		Salgado et al (2016)
quasi experimental		Methods
Sixty five infertile men between 18–50 years diagnosed with altered sperm parameters		Participants
Sixty five men received one pill (containing 250 mg <i>Tribulus terrestris</i> L.s extract) orally every 8 hours		Interventions
The effects of <i>Tribulus terrestris</i> L. on semen quality and physiological parameters		Outcomes
There was a significant difference after intervention compared to baseline and intervention group in terms of the sperm count and motility (p < 0.05) but not in sperm morphology (p > 0.05).		Results
Support for judgment	Authors' judgment	Risk of bias
There was only one intervention group and no control group	High risk	Bias
There was only one intervention group and no control group	High risk	Random sequence generation (selection Bias).
There was only one intervention group and no control group	High risk	Allocation concealment (selection bias).
There was only one intervention group and no control group	High risk	Blinding of participants and personnel (performance bias).
There was only one intervention group and no control group	High risk	Blinding of outcome assessment (detection Bias).
23 men didn't complete the study	High risk	Incomplete outcome data (attrition bias).
All outcomes were reported	Low risk	Selective reporting (reporting bias).
		Roaiah et al (2016)
quasi experimental		Methods
Thirty infertile men between 30–50 years with unexplained infertility		Participants
Thirty infertile men received 250 mg <i>Tribulus terrestris</i> L. three times a day for three month		Interventions
Effects of <i>Tribulus terrestris</i> L. on serum testosterone level (total and free), LH and semen parameters		Outcomes
<i>Tribulus terrestris</i> L. was ineffective in the treatment of idiopathic infertility (p > 0.05).		Results
Support for judgment	Authors' judgment	Risk of bias
There was only one intervention group and no control group	High risk	Bias
There was only one intervention group and no control group	High risk	Random sequence generation (selection Bias).
There was only one intervention group and no control group	High risk	Allocation concealment (selection bias).
There was only one intervention group and no control group	High risk	Blinding of participants and personnel (performance bias).
There was only one intervention group and no control group	High risk	Blinding of outcome assessment (detection Bias).
No loss	Low risk	Incomplete outcome data (attrition bias).
All outcomes were reported	Low risk	Selective reporting (reporting bias).

(continued on next page)

Table 2 (continued)

		Ismail et al (2014)
Open-labeled RCT		Methods
Sixty six infertile men between 20-55 years with oligospermia were divided in two groups including Tualang honey group (n = 34), <i>Tribulus terrestris</i> L. group (n = 32)		Participants
Intervention group: 34 participants received 20 g Tualang honey daily		Interventions
Control group: 32 participants received 250 mg Tribestan tablets three times a day		Outcomes
Evaluation the effectiveness of Tualang honey on sperm parameters, erectile function, hormonal and safety profiles		Results
There was no significant difference between Tualang honey and Tribestan groups in terms of sperm count, motility and morphology (p > 0.05).		Risk of bias
Support for judgment	Authors' judgment	Bias
They used computer block randomization based on their identification card number	Low risk	Random sequence generation (selection Bias).
This is an open-label randomized clinical trial	High risk	Allocation concealment (selection bias).
This is an open-label randomized clinical trial	High risk	Blinding of participants and personnel (performance bias).
This is an open-label randomized clinical trial	High risk	Blinding of outcome assessment (detection Bias).
Two men were excluded from the study in Tribestan group	High risk	Incomplete outcome data (attrition bias).
All outcomes were reported	Low risk	Selective reporting (reporting bias).
		Arsyad (1996)
quasi experimental		Methods
Fifty infertile men between 25-40 years with moderate idiopathic oligozoospermia		Participants
Fifty infertile men received protodioscin (Libilov) at a dose of 3 × 2 tablets / day orally for 60 days		Interventions
Evaluation the effectiveness of a certain dosage and period of administration of Libilov (protodioscin) on sperm quality and quantity and also to evaluate protodioscin's effect on libido, erection, ejaculation and orgasm		Outcomes
Libilov treatment could increase sperm count, motility and morphology in study group (p < 0.05).		Results
Support for judgment	Authors' judgment	Risk of bias
The randomization method was not described	unclear risk	Bias
No allocation concealment method was used	High risk	Random sequence generation (selection Bias).
Not blinded	High risk	Allocation concealment (selection bias).
Not blinded	High risk	Blinding of participants and personnel (performance bias).
No loss	Low risk	Blinding of outcome assessment (detection Bias).
All outcomes were reported	Low risk	Incomplete outcome data (attrition bias).
		Adimoelja et al (1995)
RCT		Methods
Forty five infertile men with oligasthenoteratospermia were divided in two groups including <i>Tribulus terrestris</i> L. group (n = 36), Placebo group (n = 9)		Participants
Intervention group: 36 participants received 500 mg purified TTL (Libilov) 3 times daily for 3 months		Interventions
Control group: 9 participants received Placebo tablets similar to <i>Tribulus terrestris</i> L.		Outcomes
Effect of <i>Tribulus terrestris</i> L. treatment on sperm parameters and acrosome reactions.		Results
There were improvements in sperm morphology in the treated group "(p > 0.05)?" and a significant increase in sperm concentration in both groups after treatment was reported without reporting p-value.		Risk of bias
Support for judgment	Authors' judgment	Bias
The randomization method was not described.	unclear risk	Random sequence generation (selection Bias).
No specific information regarding allocation concealment has been given	unclear risk	Allocation concealment (selection bias).
No specific information regarding participants and personnel blinding has been given	unclear risk	Blinding of participants and personnel (performance bias).
No specific information regarding outcome assessor blinding has been given	unclear risk	Blinding of outcome assessment (detection Bias).
There is no exact information	unclear risk	Incomplete outcome data (attrition bias).
All outcomes were not reported	High risk	Selective reporting (reporting bias).

male infertility. In the others, this plant was effective in improving some or all sperm parameters (count, motility and morphology).

T. terrestris L. is an annual herb and a medicinal plant. It is a dried fruit used for therapeutic purposes. The main chemical components of the fruit are steroidal saponins, protodioscin, tribulosaponins A and B, tribulosin and terrestrosina A–K. Other ingredients include alkaloids, tribulusamides A and B and a small amount of harman and norharman, and flavonols, such as kaempferol, quercetin and rutin. A component in this plant known as Di-p-coumaroylquinic acid leads to the activation of the antioxidant process⁴³ and also can be effective in the treatment of idiopathic male infertility through this method.¹⁵ The dominant component in the extract of this plant is protodiosine.¹⁹ This material can contain up to 45% of the dry extract of the plant (excluding macronutrient and water weight).⁴⁴ Behavioral, hematological, biochemical, functional and morphological studies on acute, subchronic and chronic

toxicity of protodiosin, which is one of the chemical components of the crude drug of this plant, observed that this substance did not show any toxicity in vitro.³⁵ Also, several studies have shown that this substance increases the number and motility of the sperms.^{40,41} Protodiosine also increases the level of testosterone and dihydrotestosterone.⁴⁵ It increases the levels of LH and testosterone and converts testosterone to dihydrotestosterone which in addition to increase libido, improves muscle development, and produces red blood cells. These changes resulting in improvement of blood circulation and oxygenation system.^{20,40}

We evaluated three parameters of sperm after treatment with *T. terrestris* L. in the included studies.

Sperm count in patients was increased.^{21,39,40} Abnormal form^{40,41} and acrosome reaction^{41,42} in infertile men, motility^{21,39,40,42} and RLP²¹ was improved. Even though, both the main drug and placebo

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Adirnoelja 1995	?	?	?	?	?	-
Arsyad 1996	?	-	-	-	+	+
Ismail 2014	+	-	-	-	-	+
Roaiah 2017	-	-	-	-	+	+
Salgado 2016	-	-	-	-	-	+
Sellandi 2012	+	+	+	+	-	+
Setiawan 1996	?	?	?	?	+	+

Fig. 2. Risk of bias summary: review authors' judgment about each risk of bias item for each included study.

increased the total sperm count, there was no statistically significant difference found between *T. terrestris* L. and placebo ($P > 0.05$) in Sellandi's study.²¹

It should have considered that the methodology of the related studies is poor. For example, only two studies had control arm with the definition of control characteristics.^{21,42} In the Arsyad's⁴⁰ study the control group and the characteristics of the number of subjects, the type of the study and the nature of placebo drug, were unknown. In the other trial, for any of the variables in the studied groups, no mean or percent had been reported.⁴¹ And in the other controlled trial *T. terrestris* L. was considered as the control arm.²⁷ The others were quasi-experimental without randomization and control arm that weakened the results of findings.³⁸

Although the majority of findings showed an improvement of some or all parameters of sperm, some of them showed that the improvement was not statistically significant³⁸ or only significant when compared before treatment's parameters.

So far, human and animal studies have been conducted on the effects of this substance on many aspects of sexuality.^{24,46} Karimi et al⁴⁷ in their study on the effect of *T. terrestris* L. extract on early spermatocytes of mouse, found that 10 mg/kg of body weight of this plant's extract increase the mean number of primary spermatocytes. In a study conducted by Hussain et al,⁴⁸ *T. terrestris* L. extract increased the serum level of testosterone in male rats. Gauthaman et al²⁴ examined the hormonal effects of *T. terrestris* L. on erectile dysfunction in sterilized primates, rabbits and rats. They showed that this plant, due to the presence of protodiosine, increased testosterone, dihydrotestosterone and dihydroepiandrosterone sulfate hormones. In another study by Keshtmand et al,⁴⁶ on the protective effects of hydroalcoholic extract of *T. terrestris* L. against Cisplatin-induced toxicity on sperm parameters in male rats, it was shown that the plant protects the testicular tissue and sperm from the destructive effects of cisplatin, due to the presence of substances such as protodiosine, flavonoids, lignin and alkaloids.

4.1. The weakness of the articles and need for further studies

Among the included trials, none of the value of the main variables was reported in percent or average, before and after the treatment.²¹ Also, in one trial, honey was chosen as the main drug and *T. terrestris* L. was considered as the control group. Since the studied plant was also considered as a treatment herb, therefore, despite the meaningful results within the group, this difference between groups was not significant, and the effect size was not reported in this study.²⁷ In the other trial, *T. terrestris* L. was considered as an intervention and a placebo tablet containing sugar. In terms of methodology, randomization and concealment of allocation and blindness were not mentioned. However, complete information was provided on the parameters of the spermiogram. One of the weak points in the report was the lack of presentation of the main variables before treatment and only post treatment results were reported in both intervention and placebo groups.⁴² In general, the quality of evidence was poor. Also, the included studies had high data heterogeneity and therefore, data pooling to conducting a meta-analysis was impossible.

Considering the limitations that exist in these studies regarding the assessment of the effect of *T. terrestris* L. on semen parameters in men with idiopathic infertility, it is suggested that further research on infertility properties should be conducted by employing suitable models with adequate controls, designed to confirm the existence of active principles in whole plant or specific parts.

This review focused on human articles and as such, it is suggested that a review be made on animal subjects in this field.

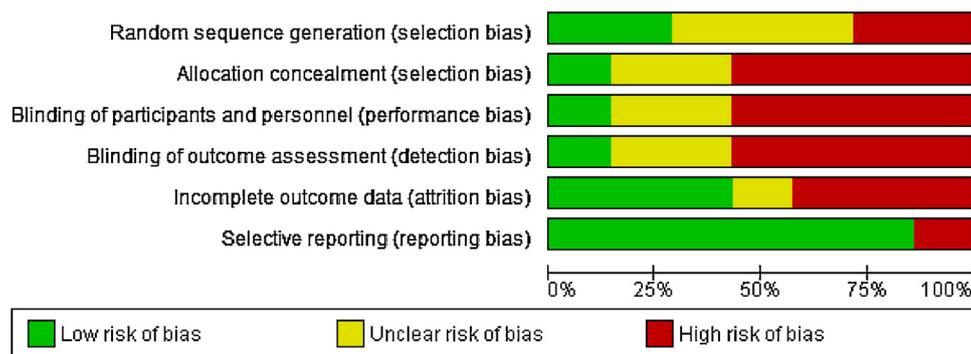


Fig. 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

5. Conclusion

The results of the review of articles showed that in total, consumption of *T. terrestris* leads to improvement in sperm parameters. But because some of the articles were not randomized control trial (they were quasi-experimental or semi-experimental) or their data were incomplete or had a high risk of bias, therefore performing proper well-designed randomized controlled clinical trials in order to determine the effect of this plant on sperm parameters seems necessary.

6. Authors' contributions

Sanagoo S: Data collection or management, Manuscript writing/editing, Protocol/ project development.

Farshbaf Khalili A: Data analysis, Manuscript writing/editing

Gassab Abdollahi N: Data collection or management, Protocol/project development

Sadeghzade Oskouei B: Data collection or management

Salehi Pourmehr H: Data analysis

Hazhir N: Data collection or management

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Conflict of interest

The authors declared no conflict of interest.

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